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**Results of cryoablation for atrial fibrillation concomitant with video-assisted
minimally invasive mitral valve surgery**

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26 **GLOSSARY OF ABBREVIATIONS**

- 27 ▪ MIMVS: minimally invasive video-assisted mitral valve surgery
- 28 ▪ AF: atrial fibrillation
- 29 ▪ MV: mitral valve
- 30 ▪ SR: sinus rhythm
- 31 ▪ TOE: trans-oesophageal echocardiography
- 32 ▪ PVs: pulmonary veins
- 33 ▪ LA: left atrium
- 34 ▪ PV: pulmonary vein
- 35 ▪ ECG: electrocardiography
- 36 ▪ SD: standard deviation
- 37 ▪ PM: pace maker
- 38 ▪ NYHA: New York Heart Association functional class
- 39 ▪ OAC: oral anticoagulation
- 40 ▪ SVC: superior vena cava
- 41 ▪ LIPV: left inferior pulmonary vein
- 42 ▪ LSPV: left superior pulmonary vein
- 43 ▪ RIPV: right inferior pulmonary vein
- 44 ▪ RSPV: right superior pulmonary vein

- 45 ■ IVC: inferior vena cava
- 46 ■ LV EF: left ventricular ejection fraction
- 47 ■ AP: antero-posterior
- 48 ■ SI: supero-inferior
- 49 ■ PAPs: systolic pulmonary artery pressure
- 50 ■ ACE-i: angiotensin-converting-enzyme inhibitor

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63 **Abstract**

64 **Objectives:** Interest in minimally invasive video-assisted mitral valve surgery (MIMVS) is rapidly
65 growing. Data on concomitant atrial fibrillation (AF) ablation to MIMVS are still lacking. The
66 present study investigates the long-term results of AF cryoablation concomitant to MIMVS.

67 **Methods:** From October 2006 to September 2014, 68 patients with mitral valve (MV) disease (age
68 65.9 ± 11.1 years, 34/68 males, Euroscore log 5.4 ± 4.5) and drug resistant AF underwent MIMVS via
69 right mini-thoracotomy and concomitant left sided AF endocardial cryoablation (Cryoflex
70 Medtronic, Minneapolis, MN, USA). Patients were independently followed by cardiological
71 outpatients visits and underwent electrophysiological study when indicated.

72 **Results:** Forty-four out of 68 patients (64.7%) underwent MV repair, 8/68 patients (11.8%) also
73 received concomitant tricuspid valve surgery. One procedure was electively converted to full
74 sternotomy (1.5%). Total clamp time was 97.6 ± 22.8 minutes. In March 2015, 60 patients were
75 alive and completed the follow-up after a mean of 3.4 ± 2.0 years following the procedure. Fourty
76 eight patients (80%) presented sinus rhythm throughout the whole follow-up. Freedom from AF
77 was respectively 96%, 87% and 72% at 1, 3 and 5 years. We recorded 2 pace-maker implants
78 (3.3%). Three patients suffered symptomatic recurrences (2 atypical atrial flutter/1 atrial
79 fibrillation) and underwent transcatheter ablation: all three patients remained in stable sinus rhythm
80 for the remaining follow-up.

81 **Conclusions:** Given the favourable long term sinus rhythm maintenance rates of concomitant
82 Cryoablation, MIMVS can also be offered to symptomatic AF patients. AF transcatheter ablation
83 may easily avoid further symptomatic recurrences.

84 Key-words: atrial fibrillation, minimally invasive mitral, surgical ablation

85

86 **Introduction**

87 Interest in minimally invasive mitral valve (MV) surgery through a video-assisted mini-
88 thoracotomy approach (MIMVS) is rapidly growing since when was first introduced in the mid-
89 1990s [1]. A number of large studies have demonstrated the feasibility of performing MIMVS
90 aiming to achieve similar safety and efficacy to conventional surgery with the added advantages of
91 reduced trauma, improved cosmesis and shorter hospitalization [2,3].

92 Atrial fibrillation (AF) is the most common cardiac arrhythmia observed in clinical practice and
93 confers an increased incidence of thromboembolic events and mortality [4]. A substantial increase
94 in the incidence of AF has been reported in patients with indications for mitral valve surgery, and
95 has also been demonstrated to be a profound risk factor for mortality [5]. The weight of this
96 evidence has provided the impetus for the combination of surgical AF treatment and core cardiac
97 surgical intervention, with the hope of synergistic improvements in both sinus rhythm (SR)
98 maintenance and risk of morbidity and mortality [6, 7].

99 Concomitant surgical AF ablation and mitral valve surgery have proved to offer improved short-
100 and mid-term SR maintenance compared to patients undergoing mitral valve surgery only. No
101 differences were found between these two groups in terms of 30-day mortality, all-cause mortality,
102 pacemaker implantation, stroke and thromboembolic events [8]. The advent of alternative energy
103 sources has greatly simplified the original öcut and sewö technique to create transmural lines
104 transforming surgical ablation into an easier, safer and faster procedure to be associated to MIMVS
105 [9, 10]. Recently published guidelines have called for long-term follow-up studies on this topic [11-
106 14]. However data on follow-up after concomitant AF ablation to MIMVS are still missing. The
107 present study investigates the long-term results of AF cryoablation concomitant to MIMVS.

108

109

110 **Materials and methods**

111 is. From October 2006 to September 2014, out of 781 MIMVS, the standard practice for MV
112 disease in our Unit since October 2006, sixty-eight patients with concomitant drug resistant AF
113 (13% paroxysmal, 87% persistent/long standing persistent) underwent video-assisted MIMVS via
114 right mini-thoracotomy through the 4th intercostal space and concomitant left sided AF cryoablation
115 (Cryoflex Medtronic, Minneapolis, MN, USA). Each patient in our study signed a written informed
116 consent to undergo surgical or transcatheter procedures. Preoperative characteristics are
117 summarized in Table 1. Patients that had already performed a cardiac surgical procedure or a
118 previous transcatheter AF ablation were not included in this series. The analysis was conducted in
119 an Academic medical center where patients accept to share their clinical data in an anonymous
120 form. The study was observational and did not add treatment or modify conventional surgical
121 procedure for the specific clinical indication. *Surgical procedure.* After a full preoperative work-up
122 that included aorto-iliac angiography/CT scan, the most appropriate out of the following three
123 MIMVS approaches was selected: direct aortic cannulation and endoaortic balloon occlusion
124 (EndoDirect, Edwards Lifesciences, Irvine, CA); femoral arterial cannulation either with endoaortic
125 balloon occlusion (EndoReturn, Edwards Lifesciences, Irvine, CA) or with transthoracic clamp
126 (Chitwood Clamp, Scanlan International Inc, St Paul, MN). All patients underwent video-assisted
127 right minithoracotomy through the 4th intercostal space (range 4-6 cm). Double lumen endotracheal
128 ventilation, transoesophageal echo (TOE) and CO₂ surgical field flooding were also used in all
129 patients. Venous return was routinely obtained by double cannulation (jugular and femoral) and
130 myocardial protection by cold crystalloid cardioplegia [15, 16].

131 Concomitant left sided AF cryoablation (Argon based Cryomaze, Cryoflex Medtronic, Minneapolis,
132 MN, USA) consisted of isolation of the pulmonary veins (PVs) and of the posterior left atrial (LA)
133 wall between the veins by a ∅ encircling cryolesion connected to the surgical paraseptal left atrial
134 incision performed for mitral exposure, eventually creating the so-called ∅box lesion (Figure 1). In

135 addition, a linear cryolesion (ömitral lineö) was performed from the previously created öbox lesionö
136 to the mitral valve annulus to block conduction across the left atrial isthmus.

137 *Electrophysiology study and transcatheter AF ablation.* Under conscious sedation, and guided by a
138 3-dimensional electroanatomic mapping system (CARTO, Biosense Webster), the LA and PVs
139 ostia were mapped measuring unipolar local voltage and detecting presence or not of PV isolation.
140 In case of evidence of conduction gap between the PV and the atrium, antral pulmonary vein
141 isolation was performed by radiofrequency ablation (Smartouch, Biosense Webster) aiming to
142 complete PV isolation extending the surgical lesion set as demonstrated by circular mapping
143 catheter (Lasso, Biosense Webster).

144 *Clinical follow-up and event definition.* After discharge patients were followed by cardiological
145 outpatient visits as for lone AF transcatheter ablation protocol [11] including clinical examination
146 and ECG at 3, 6, 12 months and then yearly. Holter monitoring was performed at least once in all
147 patients. In case of symptom recurrence between follow up visits patients were reassessed by
148 clinical examination, ECG and Holter monitoring. Electrophysiological study and transcatheter AF
149 ablation were performed when indicated. Study period was closed in March 2015, all patients with
150 at least 6 months follow up were included and reassessed with clinical examination, ECG and
151 transthoracic Echocardiography.

152 Adverse events were classified according to the standardized definitions of the Society of Thoracic
153 Surgeons/American Association of Thoracic Surgery/European Association of Cardiothoracic
154 Surgery öGuidelines for Reporting Morbidity and Mortality in Cardiac Valvular Operationsö and
155 outcomes of AF cryoablation were reported following the HRS/EHRA/ECAS Expert Consensus
156 Statement [11, 17]. A blanking period of three months was considered; following this interval any
157 AF episode, persistent or paroxysmal, was registered as an event. All events were also classified as
158 early (occurring within 30 days from the procedure) or late (>31 days after the procedure).

159 *Statistical analysis.* Categorical variables are reported as counts and percentages, while continuous
160 variables as means and standard deviations (SD). Correlations between parameters and study groups
161 were tested in cross tabulation tables by means of the Pearson Chi-Square or Fisher's Exact Test
162 and by one-way ANOVA respectively for categorical and continuous variables. McNemar's test
163 was used on paired categorical variables. Kaplan Meier curves were computed to describe AF free
164 survival over time. A two sided p-value <0.05 was considered statistically significant; all analyses
165 were performed with SPSS 20.0 (IBM Corp., Armonk, NY, USA)..

166

167 **Results**

168 Forty-four out of 68 patients (64.7%) underwent mitral valve repair. By pathology, repair rates were
169 32/37 (86.5%) degenerative, 11/15 (73.3%) functional, and 1/16 (0.6%) rheumatic. Eight patients
170 (11.8%) received also concomitant tricuspid valve surgery (Table 2). One procedure was electively
171 converted to full sternotomy (1.5%) due to unexpected severe pleural adhesions and had an
172 uneventful postoperative course. Total clamp time was 97.6 ± 22.8 minutes. There was no reopening
173 for any cause. 23/68 patients (33.8%) suffered AF relapses during hospitalization, 62 patients were
174 discharged from the Unit in SR (91.2%). One in-hospital minor stroke was recorded (1/68, 1.5%);
175 no patients required PM implantation in the acute phase. Early mortality was 1/68 (1.5%, due to
176 respiratory complications following cardiac arrest resuscitated in the Ward). In March 2015 60
177 patients completed the follow-up after a mean of 3.4 ± 2.0 years following the procedure. Study flow
178 chart following the procedure is depicted in Figure 2. In this time frame no patients required redo
179 surgery; valve repair and replacement reported favourable results (no MR 43, 63.3%; $<2+/4+$ 25,
180 36.7%). Three patients suffered from minor stroke (4.4%), while 1 patient (who relapsed on the
181 second day after surgery with permanent AF) had a stroke (1.5%). Two (3.3%) patients required
182 PM implantation during follow-up. Figure 3a illustrates echocardiographic parameters and
183 functional class at baseline and at end of follow-up. Notably mean pulmonary artery pressure (from

184 46.0 to 36.1, $p=0.006$), antero-posterior left atrial diameter (from 54.5 to 49.2, $p=0.012$) and NYHA
185 functional class (from 2.6 to 1.2, $p<0.001$) significantly decreased. Medications at baseline or
186 discharge and end of follow-up are shown in Figure 3b. At 1-year follow-up 50% of patients
187 discontinued amiodarone. Compared to discharge, significantly less patients were prescribed
188 amiodarone at follow-up (56.3% vs. 18.8%, $p<0.001$) while more patients assumed beta-blockers
189 (9.4% vs 68.8%, $p<0.001$). Oral anticoagulants were discontinued in a significant proportion of
190 patients (84.6% on OAC pre-surgery vs. 56.4% on OAC at follow-up, $p<0.001$); in particular, 13/60
191 (21.7%) patients discontinued OAC at 1-year follow-up. At 1-year follow-up freedom from AF
192 recurrences was 94.8%. Forty-eight patients (80%) presented SR throughout the whole follow up.
193 Out of the 12 patients (20%) suffering relapses, 7 patients (58.3%) suffered paroxysmal episodes
194 while 5 (41.7%) presented persistent AF (Figure 2). Seven patients (58.3%) relapsed as atypical
195 atrial flutter while 5 (41.7%) as atrial fibrillation. Overall, three patients suffered symptomatic
196 recurrences (2 atypical atrial flutter, 1 atrial fibrillation) and an electrophysiological study was
197 indicated and performed in these patients (Figure 4). In two cases arrhythmia was sustained outside
198 the lesion set while in one case a conduction gap was recorded. Following transcatheter ablation all
199 three patients resulted in sinus rhythm for the remaining follow up. Freedom from AF relapses,
200 stratified by AF type, is reported in Figure 5. Table 1 also describes preoperative characteristics of
201 the patients population completing follow-up stratified by AF relapses at univariate analysis,
202 highlighting that AF characteristics before the surgical ablation (if paroxysmal or persistent/long-
203 standing persistent) and NYHA class seem to significantly predict relapses.

204

205 **Discussion**

206 The main finding of the present study is that concomitant surgical video-assisted left sided AF
207 cryoablation creating a box lesion plus a mitral line during MIMVS resulted in favourable long-
208 term sinus rhythm maintenance rates. Out of all, only three patients suffered symptomatic

209 recurrences, with ECG documentation of atypical atrial flutter in two cases and AF in one.
210 Following transcatheter ablation, patients resulted in sinus rhythm for the remaining follow-up.
211 Based on the present experience, therefore, in the remote case of symptomatic arrhythmia relapses,
212 AF transcatheter ablation completing the surgical lesion set seems to easily avoid further
213 recurrences.

214 The cut-and-sew Cox-Maze III procedure has been the gold standard for surgical AF treatment and
215 has proved to be effective at eliminating the arrhythmia [18]. In recent years the development of
216 ablation technologies has dramatically changed the field of AF surgical ablation by the introduction
217 of new techniques and energy sources [8,9,10], allowing the replacement of the surgical incisions
218 with the linear ablation lines, transforming a technically complex procedure into an accessible and
219 minimally invasive approach. Differently from paroxysmal AF, in which triggers from the
220 pulmonary veins play an important role in the initiation of AF, in non-paroxysmal AF, atrial
221 substrate modification is thought to be highly relevant [19]. This is especially true for patients with
222 valvular heart disease, in which a dilated and remodeled atrium is present. In fact, previous studies
223 have shown that mechanisms as the elongation and stretch of the atrial fibers and the presence of
224 atrial fibrosis are crucial in the initiation and maintenance of AF in such a patients [20]. Therefore,
225 procedures aiming to isolate the PVs and to permanently modify the atrial substrate with the
226 creation of transmural linear lesions are indeed promising.

227 The principal shortcomings of the use of minimal access techniques is that, due to potential
228 suboptimal exposure, they may lead to an excess of simplification in the lesion set and potentially
229 increase the possibility of conduction gaps. In this context, electrophysiological validation may
230 permit electrical evaluation of the surgical ablation and allows to perform additional transcatheter
231 ablation when necessary [21-23]. In fact, new hybrid approaches, combining minimally invasive
232 surgical and percutaneous ablation are emerging [24].

233 Cryoablation during concomitant cardiac surgical procedures in sternotomy has appeared to be safe
234 and effective [25]. Recently Gaita et al. reported that on patients with long-standing persistent AF
235 and valvular heart disease, an hybrid approach including surgical cryoablation in sternotomy
236 patients, consisting of pulmonary veins isolation and left atrial linear lesions combined with
237 consequent transcatheter radiofrequency ablation was highly effective in maintaining very long-
238 term follow-up SR [24]. However, in this experience 21.2% of the patients needed transcatheter
239 ablation touch-ups to eliminate conduction gaps and to complete atrial lines. In the present study
240 safe and reproducible transmural lesions set in a bloodless surgical field, was achieved by an
241 endocardial argon-based cooling cryoablation system with a flexible, easily adaptable to patient's
242 anatomy cryoprobe (-160°C for 120 seconds) without the need of consequent transcatheter touch-
243 ups in the vast majority of the cases.

244 Another important issue regards the thromboembolic complications during follow up. Literature
245 reports an annual stroke rate in surgically treated valvular patients varying from 0.8% to 3%. This
246 thromboembolic risk is higher if AF is present [26,27]. In the present population, three patients
247 experienced a minor stroke and one patient had a stroke during the follow-up, giving an overall
248 annual rate of 1.7%. The maintenance of SR seems, therefore, to act as a protective factor against
249 stroke, even in a population with surgical valvular heart disease in which the risk for
250 thromboembolic events is inherently increased.

251 Eventually, although surely influenced also by the concomitant MV surgery, minimally invasive AF
252 cryoablation resulted to impact favourably the natural history of patients with MV disease and drug
253 resistant symptomatic AF as shown by a significant reduction of NYHA class, and discontinuation
254 of amiodarone and oral anticoagulants at follow up.

255 *Conclusions*

256 Surgical cryoablation concomitant to MIMVS resulted to be highly effective in maintaining SR and
257 reducing AF burden on long-term follow-up. Based on the present study population a minimally
258 invasive approach can also be offered to symptomatic AF patients. In the remote case of
259 symptomatic arrhythmia relapses, AF transcatheter ablation may easily avoid further recurrences.

260 *Study limitations*

261 The following limitations must be taken in account. First, this report is a observational study and
262 may therefore be biased by patient selection by physician in charge. Second, the limited sample size
263 may have influenced the statistical power of the analysis. Third the limited clinical events did not
264 permit multivariate analysis to detect independent inference of the study parameters. Fourth, the
265 follow-up of our study was mostly ECG-based. Being aware that a monitoring based on serial 24h
266 ECG Holter tracings or, even better, implantable recorders would be more accurate, in a mostly
267 persistent AF setting, consideration of any AF relapse, also those present only once during the
268 follow up should limit event underestimation. Eventually, given that the surgical approach
269 described is the standard and the only performed for this specific indication in our Center, no
270 comparison group is available.

271

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355 **Figure Legends**

356 **Central Picture (same as Fig. 2):** Study flow chart. AF: atrial fibrillation; EP:
357 electrophysiological.

358
359 **Figure 1.** Anatomy of the left atrium following a para-septal atriotomy for exposure of the mitral
360 valve using a left atrial lift system. Cryoablation lesion set performed in the study population
361 connected to the left atriotomy thus creating a box lesion, plus the mitral cryoline. SVC, superior
362 vena cava; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RSPV, right
363 superior pulmonary vein; RIPV, right inferior pulmonary vein; IVC, inferior vena cava. (Modified
364 from Illustrated techniques for performing the Cox-Maze IV procedure through a right mini-
365 thoracotomy, RJ Damiano Jr et al, ACS Vol 3, No 1)

366 **Figure 2.** Study flow chart. AF: atrial fibrillation; EP: electrophysiological.

367 **Figure 3. (A)** Echocardiographic parameters and functional class at baseline and end of follow-up
368 within patients completing the 3.4 ± 2.0 year follow-up. P value by Pearson Chi-Square/Fisher's
369 Exact Test or ANOVA. LV EF, left ventricular ejection fraction; AP, antero-posterior; SI, supero-
370 inferior; PAPs, systolic pulmonary artery pressure; NYHA, New York Heart Association functional
371 class. **(B)** Medications at discharge and end of follow-up in patients completing the 3.4 ± 2.0 year
372 follow-up. P value by McNemar's test. ACE-i, angiotensin-converting-enzyme inhibitor; OAC, oral
373 anticoagulation. * indicates comparison between pre-surgery and follow-up.

374 **Figure 4.** 3D electroanatomic reconstruction views: **(A)** Anteroposterior and leftlateral 3-D
375 electroanatomic reconstruction view of the left atrium and pulmonary veins showing site of
376 radiofrequency ablation (red dots) from the anterior portion of right superior pulmonary vein and
377 the septal mitral isthmus and from the left inferior pulmonary vein and the lateral mitral isthmus.
378 **(B)** Posteroanterior and right oblique (30°) 3-D electroanatomic reconstruction view of the left
379 atrium and pulmonary veins showing absence of electrical activity on all the posterior wall (effect
380 of surgical box lesion; upper part) and site of radiofrequency ablation (white dots) at the anterior

381 portion of the right superior pulmonary vein (site of conduction gap; lower part). (C)
382 Anteroposterior and leftlateral 3-D electroanatomic reconstruction view of the left atrium and
383 pulmonary veins showing the electrophysiological substrate and the site of radiofrequency ablation
384 (red dots).

385 **Figure 5.** Kaplan Meier curves for survival free from AF (persistent AF; persistent and/or
386 paroxysmal A)

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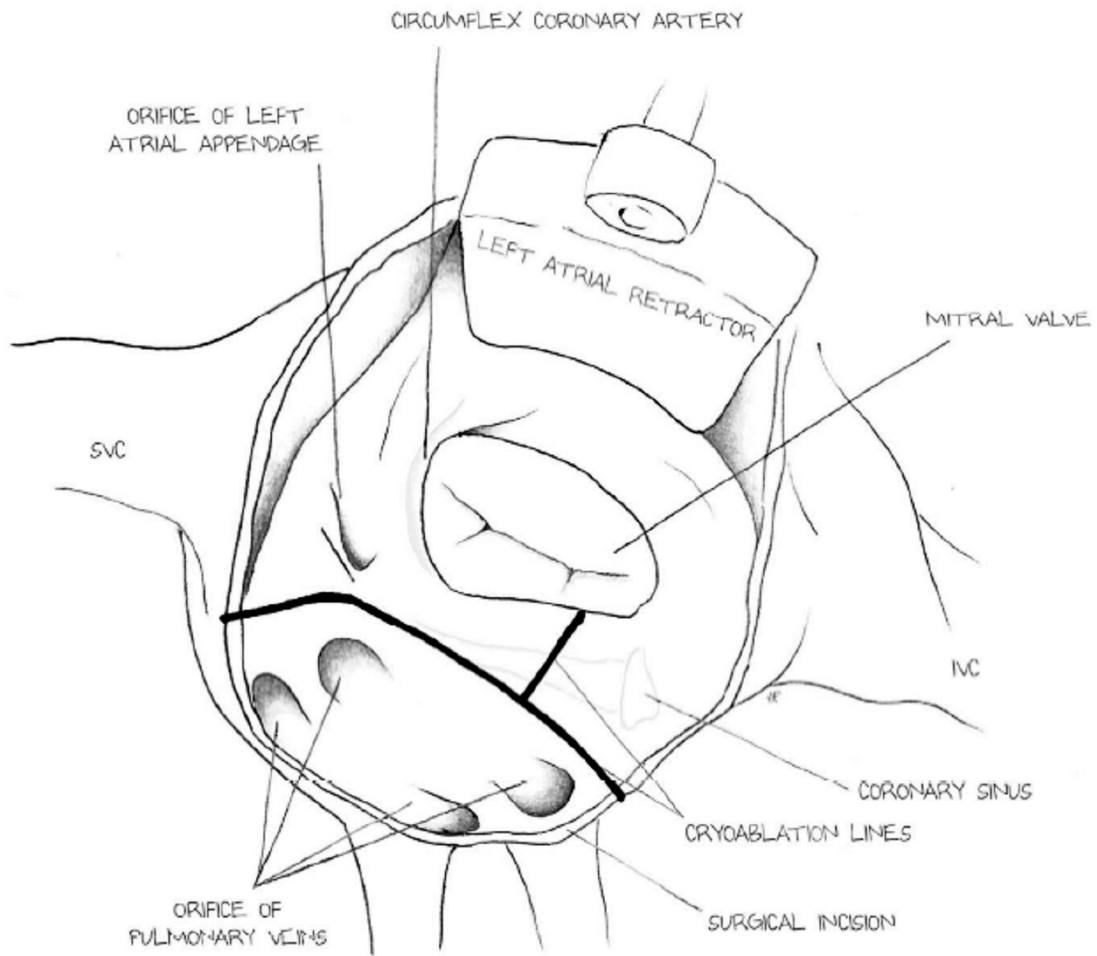
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402 Figure 1.



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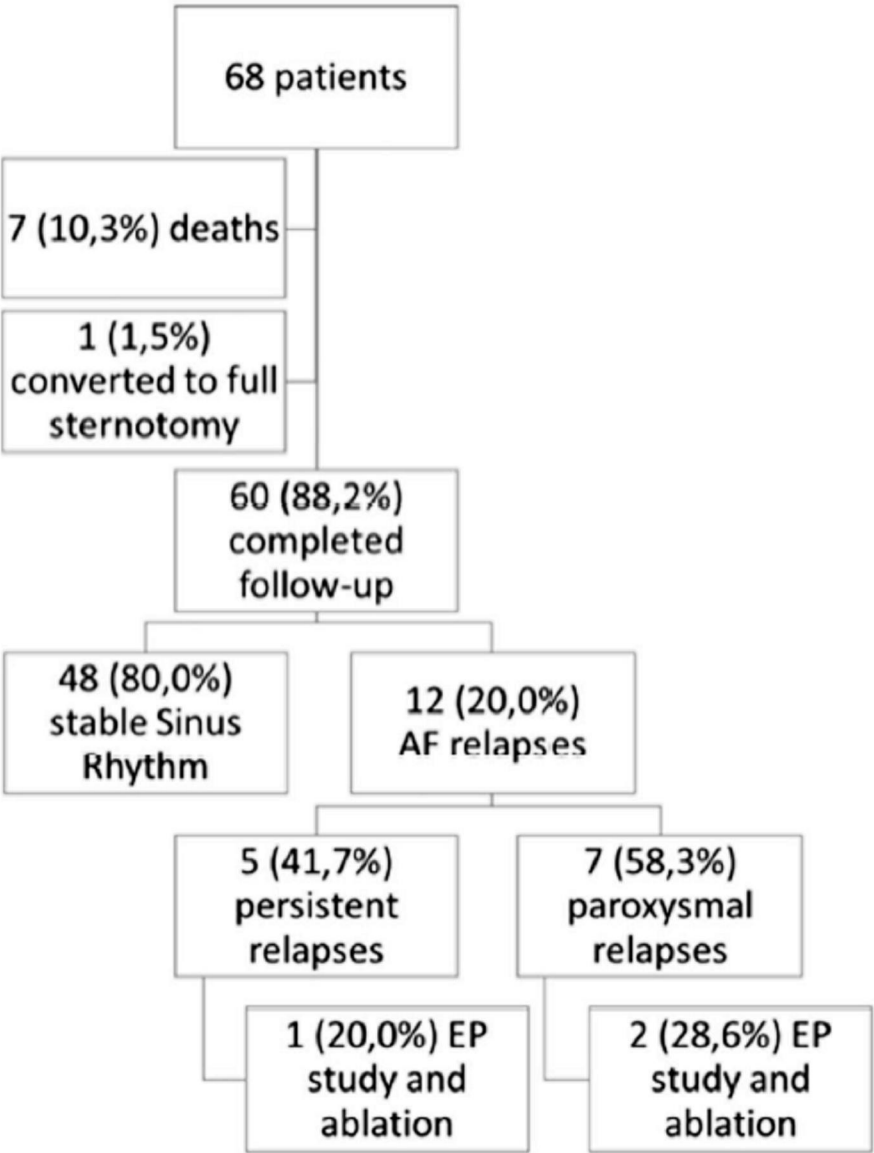
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Figure 2.



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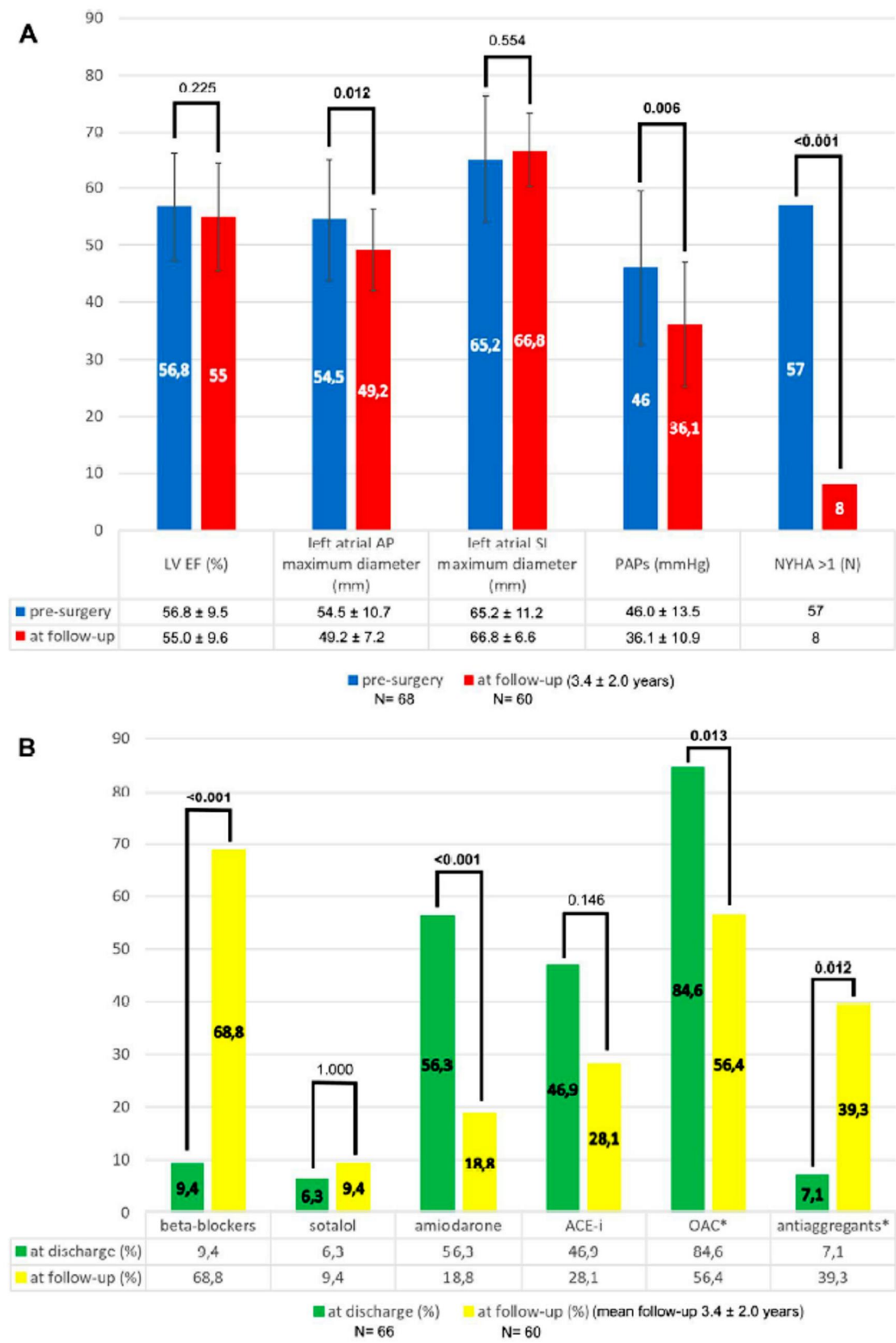
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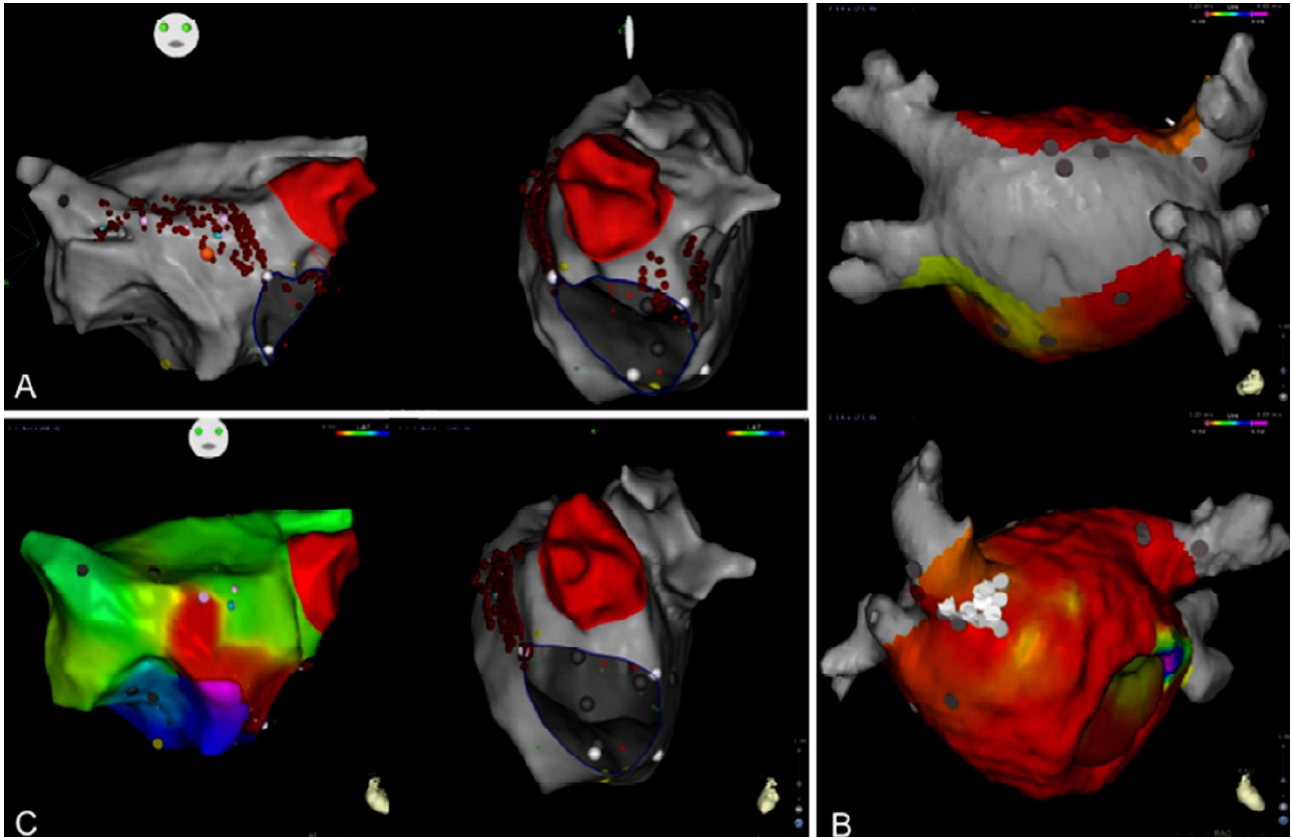
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Figure 3.



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Figure 4.



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